REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested in light of the remarks which follow.

I. CLAIM STATUS & AMENDMENTS

As correctly stated in the Office Action Summary, claims 1-19 were pending in this application when last examined.

By the present amendment, Applicants hereby cancel claim 19 without prejudice of or disclaimer as to the subject matter therein. Applicants reserve the right to file a continuation or division application on any canceled subject matter.

The present amendment also adds new claims 20-22. Support for new claim 20 can be found in the Specification, at least, at page 12, line 6 to page 13, line 10. Support for new claims 21-22 can be found in the Specification, at least, at page 9, line 25 to 10, line 10. No prohibited new matter is believed to have been added by these corrected figures.

Accordingly, upon entry of the present amendment, claims 1-18 and 20-22 will be pending in this application.

The Specification at page 5, line 25 to page 6, line 2 has been amended to recite Fig. 3A, Fig. 3B, and Fig. 3C as suggested by the Examiner. Support for this amendment can be found in the Specification, at least, at page 5, line 25 to page 6, line 2 as originally filed. No prohibited new matter is believed to have been added by this amendment.

Corrected Formal Figures 1-3 are submitted herewith that correct the deficiencies noted in Form PTO-948. Support for these corrected Figures can be found, at least, in the Figures as originally filed. Thus, no prohibited new matter is believed to have been added by these corrected figures.

II. FORMAL MATTERS

A. Drawings

The Drawings stand objected to as allegedly failing to comply with 37 C.F.R. § 1.84. See July 29, 2002 Office Action, item 3; form PTO-948. As previously noted

above, Applicants have submitted new, corrected Figures 1-3 which correct the deficiencies noted on the Notice of Draftsperson's Patent Drawing Review attached the Office Action dated July 31, 2000 (i.e., Paper No. 12). In particular, the drawings have been labeled with the appropriate figure legends (i.e., FIG. 1, FIG. 2, FIG. 3A, FIG. 3B, and FIG. 3C) and the quality of the photograph for FIG. 3 has been improved. Since this submission obviates the objection, Applicants respectfully request its withdrawal.

B. Objection to the Specification

The Specification stands objected to as allegedly failing to recite Fig. 3A, Fig. 3B, and Fig. 3C in the Brief Description of the Drawings. See July 29, 2002 Office, item 3. The current amendment hereby references these figures, and thus obviates this objection. Applicants respectfully request the withdrawal of this objection.

III. Rejection under 35 U.S.C. § 112, First Paragraph, Scope of Enablement

Claims 1-8, 11, 14-19 stand rejected under 35 U.S.C. § 112, first paragraph, because the Specification, while enabling for the treatment of viral encephalitis by administering "antibodies that bind the alpha-4 subunit of VLA-4" and "peptides of SEQ ID NOS: 3-5," purportedly does not provide enablement for "any other agent that inhibits the binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin." See July 29, 2002 Office Action, item 4. For at least all of the reasons set forth below, Applicants respectfully traverse this rejection and request its withdrawal.

A. The Scope and Enablement Issue

As to the scope of enablement, Applicants submit that the Specification fully enables the breadth of the claimed invention. The Examiner's argument appears to hinge on the ability of the Specification to teach one of skill in the art how to find structurally related or unrelated compounds that have the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. The Examiner believes that minor structural differences between among structurally related or

unrelated compounds would be expected to have different activities which is further compounded by the myriad of direct and indirect effects associated with various adhesion pathways. See July 29, 2002 Office Action, item 4.

Contrary to this position, the Specification does teach how to find and screen various agents for the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. In this regard, the Specification teaches that agents includes antibodies and small molecules, peptides, etc. These therapeutic agents function by inhibiting or preventing leukocytes bearing the alpha-4 integrin (a subunit of VLA-4) from binding to endothelial cells of the CNS, thus mediating the inflammatory process. More specifically, some therapeutic agents of the present invention bind to an epitope of alpha-4 integrin that is present when alpha-4 is associated with beta-1 in VLA-4, but absent when alpha-4 is associated with other subunits. Other therapeutic agents specifically bind to brain endothelial receptors, particuarlly, VCAM-1, that interact with alpha-4 integrin in producing an inflammatory response.

Moreover, as the Examiner has admitted, the Specification provides numerous examples of such therapeutic agents, such as antibodies that bind the alpha-4 subunit of VLA-4 (Specification, page 9, lines 11-24, and page 10, lines 11-20, page 12, lines 5-29), as well as fragments to such antibodies (Specification, page 13, lines 13-30), and peptides that have the binding affinity for VLA-4 (Specification, page 9, lines 25 to page 10, line 6), also see SEQ ID NOS: 3-5. In addition to these compounds, the Specification provides numerous methods and assays to test other potential therapeutic agents for the appropriate binding specificity and/or the capacity to block the interaction of VLA-4 receptor with inflamed endothelial cells, other cells bearing a VCAM-1 counterreceptor, or purified VCAM-1 counterreceptor. See Specification, page 8, line 12 to page 9, line 8; and page 15, lines 14-31. Thus, the Specification describes extensive teachings as to how to obtain such binding agents by producing and screening such agents for their ability to inhibit leukocytes bearing VLA-4 from binding to CNS endothelial cells. See Specification, pages 9-10, page 15, line 14 to page 16, line 4.

The Specification further discloses that the libraries of compounds can be initially screened for specific binding to the alpha-4 integrin subunit of VLA-4 or to VCAM-1, optionally in competition with a reference compound known to have blocking activity. Appropriate activity can then be confirmed using one of the assays described at pages 8 and 9 of the Specification.

Certainly such methods and assays were well within the purview of one of skill in the art at the time of the claimed invention. Likewise, such methods would not require undue experimentation. Thus, for at least these reasons, Applicants respectfully request the withdrawal of this rejection.

B. Incorporation by Reference

The Examiner alleges that Applicants appear to rely upon the disclosure of peptides disclosed in WO 96/22966, WO 96/20216, WO 96/00581, and WO 96/06108, as well as, U.S. Patent No. 5,510,332. See July 29, 2002 Office Action, item 4.

The Examiner has indicated that the peptides of SEQ ID NOs: 3-5 and the peptides in U.S. Patent No. 5,510,332 are properly disclosed in the current Specification. However, with respect to references incorporated in the instant application that disclose methods for screening reagents with the claimed binding characteristics, the Examiner believes that these teachings constitute essential subject matter, and therefore cannot be incorporated by reference.

Applicants respectfully traverse this position. First, the presently claimed invention is not directed to specific agents that inhibit leukocyte binding to endothelial cells. Instead, the claimed invention is directed to the use of such agents in treating viral encephalitis. In this regard, various reagents with the required binding characteristics are made available in the instant Specification. Second, other reagents can be identified by using various routinely practiced high throughput screening methods. Applicants submit that the identification of other reagents is well within the purview of one of skill in the art. It is well established that a Specification need not teach, and preferably omits, what is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Ind., 802 F.2d 1367, 1368,

231 U.S.P.Q. 81, 94 (Fed. Cir. 1986); In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); and M.P.E.P. § 2164.01. Third, Applicants submit that all of the these reagents are exemplary, rather than essential for the presently claimed invention. Accordingly, Applicants submit that the identity of an agent is not "essential materials" of the subject invention and that one of skill in the art could practice the claimed invention without undue experimentation given the provided examples. Therefore, withdrawal of this rejection is respectfully requested.

In the event that the Examiner decides to maintain this rejection, Applicants invite the Examiner to contact the Applicant and identify the specific subject matter that is deemed to be missing from the instant Specification.

IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 19 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite for being an omnibus type claim. See July 29, 2002 Office Action, item 5.

For the sole purpose of expediting prosecution and not to acquiesce to the Examiner's rejection, Applicants have canceled claim 19 without prejudice or disclaimer thereto. Thus, Applicants respectfully request the withdrawal of this rejection.

V. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Bendig and/or Soilu-Hanninen (1996) and/or Soilu-Hanninen (1997) in view of Ashwell

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bendig *et al.* U.S. Patent No. 5,840,299 ("Bendig") and/or Soilu-Hanninen *et al.*, SCAND. J. IMMUNOL., 43:727 (1996) ("Soilu-Hanninen (1996)") and/or Soilu-Hanninen *et al.*, J. NEUROIMMUNOL., 72:95-105 (1997) ("Soilu-Hanninen (1997)") and further in view of Ashwell *et al.* U.S. Patent No. 6,291,453 ("Ashwell"). See July 29, 2002 Office Action, item 6.

Applicants respectfully traverse this rejection for the reasons previously set forth in the Amendment and Reply entered on April 6, 2001 along with the Continuing Prosecution Application, the Declaration of Stephen J. Karlik under 37 C.F.R. § 1.132 ("Karlik Declaration"), and for the reasons set forth below. However, before turning to the rejection, Applicants herein provide a brief background section examining the etiology and pathology of multiple sclerosis and herpesvirus encephalitis.

1. **Multiple Sclerosis**

Multiple sclerosis ("MS") is a chronic demyelinating disease that is characterized pathologically by multiple areas of central nervous system ("CNS") white matter inflammation, demyelination, and glial scarring (sclerosis). The disease involves inflammatory lesions along the myelin sheath of nerve fibers in the CNS resulting in the demyelination of the myelin sheath. The disease attacks only the CNS, and the peripheral nervous system is not involved. Typically, most myelin sheaths within a lesion are destroyed and the axons are left undamaged.

MS has a **complex** etiology comprising multiple, **unidentified** susceptibility genes and environmental influences. Although numerous theories have been postulated, the cause of MS remains **unknown**. It is believed that the MS is an autoimmune disease, because of its analogy with the disease model of experimental allergic encephalomyelitis (EAE). Both MS and EAE involve immune cells attacking the myelin sheath surrounding nerves in the brain and spinal chord. EAE is induced by immunization with the myelin basic protein. Nonetheless, despite extensive research and the availability of various EAE models in laboratory rodents, the cause MS in humans has not been identified. See Sadiq *et al.*, MERRITT'S TEXTBOOK OF NEUROLOGY, Chapter 128: Demyelinating Diseases, pp. 804-29 (Rowland ed., Williams & Wilkins, Baltimore, 1995) ("Sadiq").

2. **Herpesvirus-induced Encephalitis**

Viral encephalitis is an acute febrile illness with nervous system involvement. Members of the herpesvirus group that have been associated with encephalitis include

herpes simplex, varicella-zoster, cytomegalovirus, and the Epstein-Barr virus. This group of viruses include DNA-containing viruses that contain a lipid envelope and multiply in the nucleus of the cell. Members of the group share the common feature of establishing latency in the trigeminal ganglia during the primary infection. Years later, nonspecific stimuli cause reactivation, which is usually manifested as herpes labialis (*i.e.*, cold sores).

While neurologic involvement is a rare complication of reactivation of herpesviruses, it can occur. Herpes simplex type 1 (HSV1) is the herpesvirus most often associated with viral encephalitis. Presumably, the virus reaches the brain through branches of the trigeminal nerve to the basal meninges, resulting in localization of the encephalitis in the temporal and orbital frontal lobes. During this encephalytic stage, HSV1 infects the inferomedial surfaces of the temporal and frontal lobes and causes hemorrhagic necrosis. See Jubelt *et al.*, MERRITT'S TEXTBOOK OF NEUROLOGY, Section III: Infections of the Nervous System, Chapter 23: Viral Infections, pp. 142-79 (Rowland ed., Williams & Wilkins, Baltimore, 1995) ("Jubelt").

3. The Alleged Link Between Multiple Sclerosis and Viral Infection

One controversial theory suggests a combined immunogenetic-viral cause for MS. In this regard, measles, rubella, mumps, coronavirus, parainfluenza, herpes simplex, Epstein-Barr, vaccinia, and HTLV-1 viruses all have been reported to be present in patients with MS. However, none of these agents has been reproducibly detected. Sadiq, page 8076, second column, fourth paragraph. Nor are all of these viruses considered members of the herpesvirus family. Moreover, Applicants submit the following journal articles and abstracts as evidence of the state of the art at the time of the claimed invention:

- Gilden, JAMA, 286(24): Editorial (2001) ("Gilden");
- Taus *et al.*, ACTA. NEUROL. SCAND., 101(4):224-8 (2000) ("Taus");
- Martin *et al.*, ACTA NEUROL. SCAND., 95(5):280-3 (1997) ("Martin");
- Simmons, HERPES, 8(3):60-3 (2001) ("Simmons").

While some of these abstracts and journals were published after Applicants' priority date, these references are representative of what one skilled in the art would have known on or before the time of the Applicants' claimed invention.

Gilden teaches that while many viruses and pathogens have been associated with MS, **none** has been linked to the disease. More specifically, Taus and Martin independently investigated the relationship between herpesviruses and MS. Taus looked at human herpesviruses 6 and 7 and found **no relationship** between the herpesviruses and MS. Similarly, Martin's findings also argue against a continuous disseminated herpesvirus infection in MS. Likewise, Simmons teaches that any association between herpesvirus and MS **remains controversial** and inconclusive at best.

4. General Argument as to the Obviousness Rejection

a. Previous Arguments

In the Amendment and Reply entered on April 6, 2001, Applicants previously argued that the cited prior art references fail to teach or suggest each and every element of the claimed invention. In this regard, Applicants argued that the cited references failed to teach or suggest treatment of **viral encephalitis** in patients **without MS**. Applicants further argued that there was no motivation to combine the reference teachings, because the models described in the cited references were **not predictive** of the claimed invention. Applicants submitted the Karlik Declaration as further support for these arguments.

Professor Karlik, a recognized expert with extensive expertise in the field of animal models for MS, pointed out that the animal models discussed in the cited references address the effects of anti-alpha-4-integrin in inhibiting inflammation due to EAE, a syndrome simulating MS. Professor Karlik noted that MS is an autoimmune disease and that the inflammation present in EAE models results primarily, if not exclusively, from **non-viral sources**. Professor Karlik further noted that viral inflammation could not have been addressed in the EAE model of the references, and that the EAE models were not predictive of the ability of antibodies to alpha-4 integrin to treat inflammation that is due exclusively to viral infections. See Karlik Declaration, pages 2-3. Karlik also noted that

the claimed invention is effective in suppressing the harmful effects of virally-induced inflammation without significantly suppressing the beneficial immune response and other effects that keep viral replication in check. See Karlik Declaration, page 3.

The Examiner considered Applicants' remarks entered on April 6, 2001, as well as, the Karlik Declaration, but found them unpersuasive. The Examiner appears to dismiss the Karlik Declaration because, according to the Examiner, Karlik describes the uncertainty and unpredictability of immunosuppressive agents that would be useful in inhibiting viral-induced inflammation. In this regard, the Examiner suggests that this unpredictability seems to indicate that immunosuppressive agents could effectively cause an increase in damage to the subject by eliminating the immune response that helps to clear the virus. Applicants submit that this uncertainty is at least one reason why the cited prior art fails to render the claimed invention obvious.

b. Failure to Teach Each & Every Limitation;
Lack of Suggestion to Combine

Assuming *arguendo* that the cited art disclosed the ability of certain agents to block undesired inflammation in non-viral encephalitis, one skilled in the art would **not** be motivated to use these agents to treat virus induced encephalitis for fear of eliminating the desired aspects of an inflammatory response in clearing viral infection. In other words, no motivation nor suggestion exists to apply the reference teachings to treat viral encephalitis. The claimed invention solves this problem in the art by effectively suppressing the harmful effects of virus induced inflammation without significantly suppressing the beneficial effects of inflammation that inhibit viral replication.

It is well established that the totality of the art must be considered, and a proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. See M.P.E.P. § 2145 (X)(D)(3); In re Hedges, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986). Since inflammatory responses are desirable in clearing viral infection, those skilled in the art would not be motivated to use agents that block the inflammatory response. Thus, for at least this reason, Applicants request the withdrawal of this rejection.

Furthermore, Applicants submit that Bendig fails to teach a method of treating **herpesvirus** infected patients that are **free of MS** using agents to inhibit the binding of leukocytes to brain endothelial cells via the leukocyte cell surface antigen alpha-4 integrin. Instead, Bendig relates to the use of VLA-α4-specific antibodies in the treatment of the inflammatory response of the CNS, known as MS. However there is **no** teaching that viral encephalitis could be treated. As set forth above, the etiologies and pathologies of viral encephalitis and MS are completely different. These differences are such that one skilled in the art would not believe that treatment of one condition would entail treatment of the other.

Soilu-Hanninen (1996) merely reports that HSV was present in more MS cases than control ones (i.e., 46% of MS cases and 28% of control cases have HSV-1 or HSV-2). Thus, neither reference proposes treating encephalitis in herpesvirus infected patients that are free of MS. Similarly, Soilu-Hanninen (1997) discusses the treatment of virus-facilitated EAE with VLA-4-specific mAb. However, unlike the claimed methods, Soilu-Hanninen does not discuss treatment of herpesvirus infected patients **that are free of MS**. In addition, in Soilu-Hanninen (1997), the virus which induced the EAE was Semliki Forest virus, which is an alphavirus, and not a herpesvirus as required in the claims.

The Examiner appears to rely on Bendig, Soilu-Hanninen (1996) and Soilu-Hanninen (1997) as teaching VLA-4α-specific antibodies to treat encephalitis (allegedly including herpesvirus-induced encephalitis) **and** MS. The Examiner has stated that "[w]hile the claimed methods are distinguished from MS, it **appears** that the combined teachings are consistent with the role of T cells in viral inflammation encompassing viral encephalitis." See July 29, 2002 Office Action, item 6 [emphasis added]. The Examiner further asserts that there was sufficient motivation and expectation of success based on the role of T cells in viral inflammation encompassing viral encephalitis, via the blocking of VLA-4:VCAM-1 interactions. See July 29, 2002 Office Action, item 6. However, as discussed above, such conclusory assertions contradict what was generally known in the art at the time of the claimed invention with regard to EAE, MS, and viral encephalitis.

As disclosed in the Specification and discussed above, EAE is an experimentally induced and reproducible syndrome that simulates MS and is **different** from viral encephalitis. See Specification, page 18, lines 9-12. Unlike viral encephalitis, which is caused by an inflammatory response to a systemic viral infection, MS is a complex autoimmune disease of multi-factorial origin. In this regard, the Specification at page 18, lines 13-14, clearly states that the present methods are not employed on EAE models, or humans suffering from MS.

Furthermore, as discussed above, the art at the time of the claimed invention was such that one skilled in the art would not find a credible link between MS and herpesvirus infection. Accordingly, neither EAE nor MS can be said to be predictive models of herpesvirus-induced encephalitis. One of ordinary skill in the art at the time of the claimed invention and yet today would have reasonably believed that EAE and MS are **different** and **distinguishable** from viral encephalitis. As such, EAE models and methods of treatment for MS cannot be said to have been predictive for viral encephalitis. To suggest otherwise amounts to proceeding with no reasonable expectation of success.

At best, it appears that the rejection employs an "obvious to try" rationale to arrive at the claimed invention. The rejection utilizes multiple references providing numerous hypothetical possibilities and unsubstantiated theories/choices. However, none of the references give direction as to which parameters are crucial, nor do the references indicate which one of the many possibilities is likely to succeed. Moreover, it is well established that in moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. In re O'Farrel, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988).

The Examiner attempts to rebut this argument by the addition of Ashwell as allegedly teaching that inhibitors for VLA-4:VCAM-1 interactions, including those that bind VLA-4 are useful to treat inflammatory brain disorders, such as MS, viral meningitis, and encephalitis. However, Ashwell does not specifically address herpesvirus infection. Moreover, the cited references discussed above, clearly indicate that there is no connection

between herpesvirus infection and MS and EAE. Accordingly, the addition of Ashwell amounts to nothing more than an impermissible" obvious to try" rationale.

Thus, the presently claimed methods are not obvious over the cited references in part, because the cited art fails to teach or suggest **all of the elements** of the claimed invention. Further, the cited references do **not** provide a reasonable expectation of success that the use of agents against VLA-4 would be useful in treating viral encephalitis in human patients. Accordingly, the cited references fail to render the claimed invention obvious. Therefore, Applicants respectfully request the withdrawal of this rejection.

B. Bendig and/or Soilu-Hanninen (1996) and/or Soilu-Hanninen (1997) in view of Ashwell and in view of Planz and/or Sanders and/or Editorial

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bendig *et al.* U.S. Patent No. 5,840,299 ("Bendig") and/or Soilu-Hanninen *et al.*, SCAND. J. IMMUNOL., 43:727 (1996) ("Soilu-Hanninen (1996)") and/or Soilu-Hanninen *et al.*, J. NEUROIMMUNOL., 72:95-105 (1997) ("Soilu-Hanninen (1997)") and further in view of Ashwell *et al.*, U.S. Patent No. 6,291,453 ("Ashwell"), and further in view of the art known role or etiology of various viruses including encephalitis, as evidenced by Planz *et al.*, J. VIROL., 68:896-903 (1995) ("Planz") and/or the role of herpesviruses in MS as evidenced by Sanders *et al.*, ARCHIVES OF NEUROLOGY, 53:125-133 (1996) ("Sanders 1") and/or Editorial, ARCHIVES OF NEUROLOGY, 53:123-124 (1996) ("Sanders 2"). See July 29, 2002 Office Action, item 6.

Applicants respectfully traverse this rejection for the same reasons noted above. Bendig, Soilu-Hanninen (1996), Soilu-Hanninen (1997), and Ashwell fail for the reasons discussed above. The secondary references do not cure the defects inherent to the primary references and do not teach the claimed invention when viewed alone.

The Examiner relies on Planz, Sanders, and the Editorial as allegedly providing the requisite motivation to apply the claimed treatment to patients with viral encephalitis, in particular, to patients herpesvirus induced viral encephalitis. However, as discussed above, Gilden, Taus, Martin, and Simmons clearly teach that there is no link between

herpesvirus and MS. Thus, MS and its animal model, EAE, cannot then be said to be predictive of viral induced encephalitis (i.e., immune-induced inflammation). One of ordinary skill in the art at the time of the claimed invention would have reasonably believed that EAE and MS are **different** and **distinguishable** from viral encephalitis. As such, EAE models and methods of treatment for MS cannot be said to have been predictive for viral encephalitis. Thus, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: December 30, 2002

Attachment to Amendment and Reply

Marked-up Copy of Specification

([bracketed] items deleted; underlined items added)

Marked-up Copy of the Paragraph at page 5, line 25 to page 6, line 2

-- Fig. 3: Reduction in inflammatory responses to BDV in brain from rats treated with an anti-alpha-4 integrin monoclonal antibody (day 30 post BDV-inoculation). [(A)] Fig. 3A BDV-infected rat brain showing extensive perivascular cuffing (arrow); [(B)] Fig. 3B BDV-infected rat brain showing a reduction in perivascular cuffing following anti-alpha-4 integrin monoclonal antibody treatment (arrow); [(C)] Fig. 3C uninfected rat brain control without encephalitis (arrows). Hematoxylin and eosin stain; magnification, X200.--